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Effectiveness of Stress-Reducing Interventions on the Response to Challenges to the Immune System: A Meta-Analytic Review

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Keywords

Immune system · Stress-reducing psychological interventions · Psychophysiological challenges · In vivo immune measures · In vitro immune measures

Abstract

Background: There is consistent evidence showing an interplay between psychological processes and immune function in health and disease processes. ***Objectives:*** The present systematic review and meta-analysis aims to provide a concise overview of the effectiveness of stress-reducing psychological interventions on the activation of immune responses in both healthy subjects and patients. ***Methods:*** Included are 3 types of challenges: in vivo, in vitro, and psychophysiological. Such challenges are designed to mimic naturally occurring immune-related threats. ***Results:*** A systematic literature search was conducted using PubMed, EMBASE, and PsychInfo, resulting in 75 eligible studies. The risk of bias was assessed with the Cochrane risk-of-bias tool. Across all studies, a small-to-medium effect size was found for the effects of psychological interventions on optimization of the immune function (g = 0.33; 95% CI 0.22–0.43). While the largest effects were found for in vivo immune-related challenges (g = 0.61; 95% CI 0.34–0.88; especially on studies that incorporated skin tests and wound healing), studies incorporating psychophysiological challenges and in vitro immune-related stimulations similarly suggest more optimal immune responses among those receiving stress-reducing interventions (g = 0.28; 95% CI 0.15–0.42). ***Conclusion:*** These findings showed substantial heterogeneity depending on the type of challenge, the study populations, and the intervention types. These data demonstrate support for the effectiveness of stress-reducing psychological interventions in improving immunity in studies that tested immune function by means of incorporating an in vivo, in vitro, or psychophysiological challenge. Future research should more consistently incorporate challenges into the study design to gather more insights in the mechanisms underlying the optimized immune function following a psychological intervention. This is also relevant for clinical practice, as psychological interventions can possibly supplement, or at least partially replace, current drug treatments in various somatic conditions to reduce side effects.

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Introduction

Psychosocial features can influence clinical outcomes [1–3]. More specifically, stressful events can influence the functioning of the immune system [4–6]. Several systematic reviews and meta-analyses have overall shown that particularly chronic stress suppresses protective immune responses and promotes pathological immune responses, including inflammatory responses [7–12]. Moreover, stress-related disorders, including anxiety and depression, also turned out to be associated with affective-related deficits through immune alterations [13]. These immune alterations can be expressed as slower wound healing [8, 9], impaired responses to vaccines [7], and progression of infectious and immune-mediated diseases [7, 14, 15].

Various psychological interventions, including cognitive behavioral therapy [16], mindfulness [17–21], and relaxation [17], have been found to effectively reduce stress. Therefore, it has been argued that such stress-reducing interventions may help to counteract the adverse effects of stress on immune functioning. A previous meta-analysis, however, found little support for an immune-optimizing potential of psychological interventions [22]. Some supporting evidence was provided by studies using conditioning and hypnosis interventions, although the results were heterogeneous. Due to substantial variation in immune outcomes, the generalizability was uncertain [22]. More specifically, the immune outcomes in these studies varied from counting white blood cell subsets to evaluating cell function by activating the immune system by either in vitro (i.e., exposing isolated white blood cells to an immune-activating stimulus) or in vivo (i.e., stimulating an immune response in the intact person; e.g., vaccination) methods. Each of these methods provides a different window and type of information on the functioning of the immune system. Counting cells in a resting state provides information on the number of immune cells in the circulation. However, the circulation represents only a small and selective proportion of the total cell population, it is highly dynamic within individuals, and the normal range of adequate cell numbers is rather broad. Therefore, in somatically healthy participants cell counts are of uncertain clinical significance. On the other hand, the response of the immune system to activating stimuli is considered a more representative estimate of a person's ability to mount an adequate immune response in the face of a natural challenge and may be considered a more biologically valid marker of immunocompetence [23].

In vitro activations include natural killer cell activity (NKCA), a stimulated lymphocyte proliferation response (LPR), and stimulated proinflammatory and anti-inflammatory cytokine production (i.e., chemical challenges), whereas in vivo stimulations include hypersensitivity responses to skin tests, the time of healing of a biopsy wound, or the extent to which a vaccine produces antibodies (i.e., physical challenges). In addition to the above-mentioned in vitro and in vivo activations of the immune system, psychosocial stress can also challenge the immune system [4, 5, 24, 25]. Therefore, a number of studies have evoked psychosocial stress in their participants by exposing them to psychophysiological challenges, i.e., challenges that have the potential to evoke a psychophysiological stress response, including exposure to a psychosocial stress task, to obtain additional information on how stress-reducing psychological interventions may optimize the extent to which the immune system responds to these challenges [26]. A recent systematic review provided support for the effectiveness of psychological interventions in optimization of wound healing [27]. There is, however, no recent examination of the effectiveness of stress-reducing interventions on a broader range of immune challenges, also taking psychophysiological challenges into account.

In the last few decades, studies have evaluated how the immune system responds to chemical, physical, and psychophysiological challenges after undergoing a stress-reducing psychological intervention. Previous systematic reviews and meta-analyses, including the systematic review and meta-analysis of Miller and Cohen [22] in the previous century, have already summarized the effectiveness of psychological interventions on immune function [20, 27]. This study incorporated various outcome measures that were assessed during resting states or after a challenge. However, the focus of this previous study was not on challenges per se and it did not assess the immune response after psychophysiological challenges. It can be presumed that exposing participants to different kind of challenges, i.e., chemical, physical, or psychophysiological, provides more insights in the actual responsiveness of the immune system to a natural challenge compared to assessing resting state outcomes. Therefore, the aim of the current systematic review and meta-analysis is to summarize the effectiveness of stress-reducing psychological interventions directed at optimizing immune function, focusing on studies incorporating various in vivo or in vitro immune-related and/or psychophysiological stimulations/challenges into the study design. We expected that after a stress-reducing psychological intervention participants would show a more optimized immune response to challenges as compared to participants who did not receive a stress-reducing psychological intervention. More specifically, after the

stress-reducing psychological intervention we expected a higher NKCA, higher anti-inflammatory cytokine responses, lower proinflammatory cytokine responses, higher LPR, higher antibody responses, and higher delayed-type hypersensitivity responses, as well as faster wound healing. We analyzed the pooled effects of the 3 types of challenges together as well as separately.

Methods

This systematic review and meta-analysis was performed according to PRISMA criteria [28] and it was registered in PROSPERO (registration No. CRD42017055722).

Inclusion and Exclusion Criteria

Studies were included when they met the following inclusion criteria according to PICO criteria [29]: (P) incorporation of human participants (patients or healthy participants); (I) a stress-reducing psychological intervention (which was defined as having cognitive behavior change techniques [30] as the main component, i.e., duration of more than 50% of the intervention time, such as psychotherapy, mindfulness, or relaxation) – interventions that combined psychological intervention components with physical intervention components were only included when the focus of the intervention was on the psychological components, i.e., more than 50% of the intervention; (C) incorporation of at least 1 control group without a stress-reducing psychological intervention; and (O) inclusion of immune outcome measures assessed in blood or saliva (e.g., quantification of cytokines and lymphocytes) as well as incorporation of immune-related and/or psychophysiological challenges into the study design which were assessed after the start of the stress-reducing psychological intervention. Articles were excluded when they assessed immunological functioning not by objective measurements or parameters, but when they were, for example, solely based on self-reports (e.g., self-reported infection), when they were based on case studies, or when they had insufficient methodological or statistical details about the immune or psychophysiological challenges or results (e.g., conference abstracts).

Literature Search Strategy

A systematic search was conducted using the databases PubMed, EMBASE, and PsychInfo until January 26, 2017. The search terms included Medical Subject Headings (MeSH) and words from title/abstract (tiab) as qualifiers, classified in 3 categories: stress-reducing psychological interventions, immune function, and immune-related as well as psychophysiological challenges (for the search strategy per database, see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000501645). All retrieved references were loaded into Endnote and 2 independent reviewers (L.S. and P.C.) screened the titles, abstracts, and subsequently full texts when appropriate regarding study eligibility and relevance. The reference lists of the included studies were additionally searched for potential eligible studies.

Data Extraction

A data extraction form was used to extract relevant data from the eligible studies. The extracted information for each study included: study population (e.g., healthy participants or patients); participant demographics; details of the intervention and control conditions; study methodology; incorporated chemical, physical, and/or psychophysiological challenges; immune outcome parameters; relevant outcome data; statistical analyses; and relevant information concerning the methodological quality assessment. The information was extracted by the 2 reviewers (L.S. and P.I.C.) independently. Discrepancies were identified and resolved through discussion by involving one or more additional reviewer(s) (D.S.V., J.A.B., and A.W.M.E.).

Methodological Quality Assessment in the Included Studies

Two reviewers (L.S. and P.I.C.) furthermore independently assessed the risk of bias (RoB) of the included studies using the Cochrane RoB tool [31]. The biases that were assessed included: selection bias (process of randomization and concealment of allocation), performance bias (blinding of participants and research personnel), detection bias (blinding of outcome assessment), reporting bias (handling of missing data), and attrition bias (description of reasons for withdrawal in all conditions). Biases were classified as being low, high, or unclear. Disagreements between the review authors regarding the RoB in particular studies were resolved by discussion, with involvement of a third review author (D.S.V.) if necessary.

Data Analyses

Data were analyzed using Comprehensive Meta-Analysis software version 3.3.070 (Biostat, Englewood, CO, USA). Hedges' g was the effect size metric that was applied in the descriptive statistics of this study. The effect size was calculated by subtracting the pre- from the post-immune outcome parameters in the control group and subsequently subtracting this difference score from the difference score in the intervention group, divided by the pooled SD and weighted across the number of subjects in each group. Effect sizes of 0.2 can be considered small, whereas 0.5 and 0.8 can be considered medium and large, respectively [32]. For the included studies performing within-subjects comparisons, the pre-post correlation coefficient could not be derived and therefore a correlation coefficient of $r = 0.05$ was imputed. In case a study containing multiple conditions with eligible psychological interventions, these groups were combined into a single pairwise comparison, according to the recommendations of the Cochrane handbook [31]. The pooled effects were analyzed using a random-effects model. Heterogeneity was assessed by evaluating the I^2 statistic and by visual inspection of the forest plot. Values of $I^2 = 25$, 50, and 75% can be interpreted as low, moderate, and high heterogeneity, respectively. In cases in which the results of a study were based on postintervention scores only (e.g., in the case of wound healing studies), the effect size was based on the postintervention scores. When the descriptive statistics were not available authors were requested to provide those data, and when the data were not provided alternative methods were used to calculate the effect size (e.g., using reported statistics, reported mean change scores, etc.). When studies reported that the results were not significant, without further specification of the outcomes, effect sizes were computed assuming no differences between the groups ($r = 0.00$). Because this is a rather conservative strategy that had to be applied to a substantial proportion of the data (i.e., imputation was used in 23.8% of the cases), meta-analyses were performed with and without those studies in order to evaluate the potential bias of this

method. All immune outcomes were scaled in the direction of positive Hedges' *g* representing an optimized immune function. More specifically, a higher NKCA, higher anti-inflammatory cytokine responses, lower proinflammatory cytokine responses, higher LPR, higher antibody responses, and higher delayed-type hypersensitivity responses, as well as faster wound healing, were interpreted as optimized immune outcomes.

The pooled effects of all 3 different types of challenges (i.e., in vitro immune-related stimulations, in vivo immune-related challenges, and psychophysiological challenges) were analyzed together and separately. The in vitro immune-related stimulations were subsequently subcategorized into NKCA, stimulated LPR, and stimulated cytokine production. In vivo immune-related challenges were subdivided into wound healing, vaccine responses, and immediate as well as delayed-type hypersensitivity responses after skin tests. In vivo psychophysiological challenges were further subdivided into acute and more protracted stress challenges, separately for plasma numbers of lymphocytes (i.e., enumeration of CD4, CD8, and CD56 numbers) and cytokines (i.e., quantification of IL-1β, IL-6, IL-8, and TNF-α). When the outcomes of in vitro stimulations were assessed on multiple concentrations of the stimulus (e.g., multiple effector-to-target ratios to evaluate NKCA or various dilutions to evaluate LPR), the effect size was derived from the concentration that most optimally differentiated conditions (i.e., the stimulus concentrations that showed the largest differences). Planned subset analyses evaluated the effects of different types of challenges within a specific category.

Data of at least 3 studies had to be available in order to conduct a meta-analysis. Sensitivity analyses were performed concerning the reliability of the results in that it was investigated whether the results would remain comparable when taking RoB and publication bias into account. In order to assess the stability of the overall effect size, it was investigated whether the effects were similar when studies with a substantial RoB (i.e., studies containing at least 1 classification of high RoB) were excluded from the analyses. In addition, publication bias was assessed by inspection of the funnel plot and applying the trim-and-fill method of Duval and Tweedie [33].

Results

Search Results

Online suppl. Figure 1 shows the flow chart of the systematic search and study selection. A total of 19,780 studies (including duplicates) were found by searching PubMed, EMBASE, and PsychInfo. After removing duplicates and screening the studies on title and abstract, 138 articles were examined in full text by the 2 independent reviewers. Of those, 65 articles fulfilled the inclusion criteria. Screening of the reference lists of the included articles yielded 9 additional eligible studies, which were not identified in the primary search as most of these studies did not specify immune outcome measures in the title and/or abstract. In total, 75 studies reported in 74 articles were included.

Study Characteristics

A total of 4,141 participants took part in the 75 studies. Detailed information concerning the study characteristics and incorporated psychological interventions are described in online suppl. Table 2. The total individual study sample size varied between 12 [34] and 252 subjects [35] (mean = 57, SD = 48). In 29 studies (38.7%), healthy volunteers were included as the study population [34, 36–62]. Other samples included patients or vulnerable adults, e.g., patients with various types of cancer [63–82], patients with HIV infection [35, 83–87], patients with rheumatoid arthritis [26, 88–90], older adults [91–94], patients with asthma/allergies [95–97], widows/women who had lost a close relative to cancer [98, 99], patients with ulcerative colitis [100, 101], women with depression after bypass surgery [102], patients with late-life insomnia [103], women suffering from infertility [104], veterans [105], and patients who had undergone surgery [106]. The mean age of the participants varied between 18.5 and 78.8 years. Details on age were not provided in 7 studies (9.3%). Twenty-four studies (32.0%) only included female participants, whereas 9 studies (12.0%) only included male participants. In 36 studies (48.0%), both males and females were included. Details on gender were not reported in 6 studies (8.0%).

RoB Assessment

Online suppl. Figure 2 presents the RoB graph and online suppl. Figure 3 the RoB summary. Of the 75 studies, 68 (90.7%) did not provide sufficient details on the methods used to randomize participants and 71 articles (94.7%) did not sufficiently specify the methods of allocation concealment (unclear RoB). RoB on performance was low for 2 articles (2.7%) due to adequate blinding procedures. In 9 articles (12.0%), participants and/or personnel were aware of the group allocation, which could have led to performance bias (high RoB). For 26 articles (34.7%), the RoB concerning a lack of blinding of participants and personnel was low. In 35 articles (46.7%), the drop-out rates and reasons for drop-out were sufficiently described and unrelated to the study outcomes, which resulted in a low RoB evaluation regarding incomplete outcome data. No study protocol was available for 73 articles (96.1%), resulting in an unclear RoB regarding selective reporting.

Type of Stress-Reducing Psychological Interventions

In total, 82 stress-reducing psychological interventions were evaluated in the 75 studies. Most interventions (28 interventions; 34.1%) were based on relaxation or stress management. Multicomponent cognitive-behavioral interventions, including psycho-education and

various cognitive and behavioral techniques, were also common and assessed in 18 cases (22.0%). Other interventions were based on manualized mindfulness and/or meditation (13 interventions; 15.9%), hypnosis (12 interventions; 14.6%), emotional disclosure (7 interventions; 8.5%), and counseling (4 interventions; 4.9%). The interventions varied in their total duration from a single session to multiple sessions over a period of 12 months.

Regarding the guidance of the interventions, all interventions included face-to-face or telephone appointments, except for 2 interventions that relied on self-practice. Of the guided interventions, 48 (58.5%) also encouraged self-practice.

Overall Immune Effects

Detailed information concerning the immune-related challenges and outcomes for each study is presented in online suppl. Table 3.

When performing an overall random-effects meta-analysis on the data, i.e., irrespectively of the incorporated challenge, an overall small effect size was found (k = 84, g = 0.33; 95% CI 0.22–0.43), with moderate heterogeneity across the studies (I^2 = 59.41%). When excluding the studies that were set at r = 0.00, a slightly higher overall small effect size was found (k = 64, g = 0.43; 95% CI 0.30–0.55, I^2 = 67.69%).

Exploratory Analyses for Participants with and without Somatic Conditions

For studies that incorporated patients with somatic conditions, a small overall effect size was found (k = 40, g = 0.34; 95% CI 0.17–0.52), with moderate heterogeneity across the studies (I^2 = 71.94%).

For studies that incorporated participants without somatic conditions, also a small overall effect size was found (k = 44, g = 0.31; 95% CI 0.20–0.43), with low heterogeneity across the studies (I^2 = 34.10%).

In vitro Immune-Related Stimulations

Of the 75 studies, 52 (68.4%) incorporated at least 1 in vitro immune stimulation test, including NKCA (32 studies), LPR (28 studies), cytokine production (10 studies), and monocyte chemotaxis (1 study).

Online suppl. Figure 4 presents the forest plot on the random-effects meta-analysis for in vitro immune-related stimulations. Overall, a small effect size was found (k = 52, g = 0.28; 95% CI 0.15–0.42), with moderate heterogeneity across the studies (I^2 = 61.43%). After excluding the studies that were set at r = 0.00, a small effect size was found (k = 39, g = 0.39; 95% CI 0.22–0.56, I^2 = 70.75%). When looking at specific subgroups of in vitro immune stimulation tests, we found a small effect size for NKCA (k = 31, g = 0.21; 95% CI 0.06–0.35, I^2 = 40.22%), LPR (k = 28, g = 0.35; 95% CI 0.13–0.57, I^2 = 73.07%), and cytokine production (k = 9, g = 0.32; 95% CI 0.14–0.51, I^2 < 0.01%).

Exploratory Analyses for Participants with and without Somatic Conditions

For studies that incorporated patients with somatic conditions, a small effect size was found (k = 33, g = 0.28; 95% CI 0.10–0.46), with moderate heterogeneity across the studies (I^2 = 69.54%).

For studies that incorporated participants without somatic conditions, also a small effect size was found (k = 19, g = 0.28; 95% CI 0.08–0.48), with low heterogeneity across the studies (I^2 = 33.76%).

In vivo Immune-Related Challenges

In vivo immune-related challenges, including skin testing (8 studies), vaccination (5 studies), and wound healing (4 studies), were incorporated into the study designs of 17 studies (22.4%).

Online suppl. Figure 5 presents the results of the random-effects meta-analysis on the pooled effects of in vivo immune-related challenges. A medium effect size was found (k = 17, g = 0.61; 95% CI 0.34–0.88), with high heterogeneity across the studies (I^2 = 74.59%). After excluding the studies that were set at r = 0.00, a similar medium effect size was found (k = 15, g = 0.64; 95% CI 0.35–0.92, I^2 = 76.73%). When looking at specific subgroups within the in vivo immune-related challenges, a large effect size was found for studies using skin tests (k = 8, g = 0.80; 95% CI 0.30–1.30, I^2 = 80.72%). Furthermore, a small effect size was found for vaccine studies (k = 5, g = 0.37; 95% CI –0.17 to 0.90, I^2 = 77.69), and a medium effect size was found for wound healing studies (k = 4, g = 0.75; 95% CI 0.45–1.05, I^2 < 0.01%).

Exploratory Analyses for Participants with and without Somatic Conditions

For studies that incorporated patients with somatic conditions, a high effect size was found (k = 4, g = 1.5; 95% CI 0.4–2.7), with high heterogeneity across the studies (I^2 = 86.973%).

For studies that incorporated participants without somatic conditions, a medium effect size was found (k = 17, g = 0.61; 95% CI 0.34–0.88), with moderate heterogeneity across the studies (I^2 = 74.59%).

Most studies were based on skin testing. Of the 4 studies that included patients with somatic conditions, 3 stud-

ies included allergic patients who were exposed to skin tests, and yielded high effect sizes ($k = 3$, $g = 2.02$; 95% CI –0.03–4.06). Five studies were found that included participants without somatic conditions. When these study findings were compared to the patients with somatic conditions, small effect sizes were found ($k = 5$, $g = 0.28$; 95% CI 0.05–0.51).

Psychophysiological Challenges

In 16 studies (19.7%), a psychophysiological challenge was incorporated; acute challenges included a speech task, exams, a cold pressor test, and a treadmill exercise test (10 studies), and challenges of a more protracted character, including academic stress and HIV serostatus notification (6 studies).

In online suppl. Figure 6, the results of the random-effects meta-analysis on the pooled effects of psychophysiological challenges is shown. One study was not included in the meta-analysis as the outcomes of that study were not based on plasma measurements, T-cell enumeration, or cytokine quantification. Overall, no effect was found ($k = 15$, $g = 0.18$; 95% CI 0.01–0.35, $I^2 < 0.01$), whereas a small effect size was found when excluding the studies that were set at $r = 0.00$ ($k = 10$, $g = 0.28$; 95% CI 0.07–0.49, $I^2 < 0.01$). When assessing studies that incorporated enumeration of lymphocyte subsets after a psychophysiological challenge (i.e., CD4, CD8, and CD56), a small effect size was found for studies incorporating a more protracted stress challenge ($k = 4$, $g = 0.33$; 95% CI = –0.06 to 0.72, $I^2 = 1.68\%$). For acute stress challenges, there were not enough studies available that had incorporated those markers in order to evaluate the effects after an acute stress challenge ($k = 2$). For studies that incorporated plasma cytokine measurements (i.e., IL-1β, IL-6, IL-8, and TNF-α) after a psychophysiological challenge, a small effect size was described in studies incorporating an acute challenge ($k = 4$, $g = 0.22$; 95% CI –0.04 to 0.49, $I^2 < 0.01\%$), whereas no studies incorporated those markers to evaluate the effects after a more protracted stress challenge.

Exploratory Analyses for Participants with and without Somatic Conditions

For studies that incorporated patients with somatic conditions, no effect was found ($k = 3$, $g = 0.11$; 95% CI –0.21 to 0.42), with low heterogeneity across the studies ($I^2 < 0.01\%$).

For studies that incorporated participants without somatic conditions, also no effect was found ($k = 12$, $g = 0.22$; 95% CI 0.01–0.42), with low heterogeneity across the studies ($I^2 < 0.01\%$).

Sensitivity Analyses

RoB within Studies

When studies with a presumed high RoB were excluded from the analyses, 23 of 84 outcomes were excluded. However, the overall effect size was not substantially altered ($k = 61$, $g = 0.34$; 95% CI 0.20–0.48).

Publication Bias

The funnel plot is displayed in online suppl. Figure 7 and suggests the presence of publication bias. The trim-and-fill method indicates that 12 studies were expected to be missing with below-average effects, as indicated by the black dots. When imputing those studies, the effect size decreased to $g = 0.21$ (95% CI 0.09–0.32).

Discussion

Over the last few decades, studies have evaluated the effectiveness of stress-reducing psychological interventions on immune function by incorporating chemical, physical, and psychophysiological challenges into the study design. These challenges are thought to present a biologically more valid reflection on the effectiveness of stress-reducing psychological interventions in optimization of the immune function as compared to unstimulated quantitative immune outcomes [23, 107, 108]. The present systematic review and meta-analysis summarized immune-related outcomes after a chemical, physical, or psychophysiological challenge following a stress-reducing psychological intervention in both healthy subjects and patients.

Overall, the findings demonstrated a small (heterogeneous) positive effect size for optimization of the immune function. As a conservative method was applied to handle studies that reported no significant results without further specifying the actual group differences, the overall effect size possibly represents a slightly underestimated effect size. While the largest effects were found for in vivo immune-related challenges (especially in studies that incorporated skin tests and wound healing), studies incorporating psychophysiological challenges and in vitro immune-related stimulations similarly suggest more optimal immune responses among those receiving stress-reducing interventions.

When focusing on in vitro immune-related stimulations, small effect sizes were found. Studies were highly diverse regarding the source of material and technical details of the stimulation. For example, studies varied in the target of stimulation (e.g., stimulation of T cells and NK

cells), the types of outcomes (e.g., proliferation, cytokine production, and killing monocytes) and the types of concentrations and the duration of stimuli. Likewise, a subset of studies stimulated whole blood, thereby performing tests in a biologically normal blood-plasma context, whereas others stimulated peripheral blood mononuclear cells, whereby tests are performed in artificial buffer solutions. Therefore, whole blood stimulations comprise a rather diverse range of cell populations (e.g., neutrophils, eosinophils, etc.), whereas the cell populations in peripheral blood mononuclear cells are more well-defined, resulting in different environments of stimulation. In addition, important details such as the concentrations used or which type of immune cells were stimulated, were often lacking from the Methods section, while such aspects may substantially influence the results. Future studies are therefore encouraged to report more carefully on the methodological details. This could, for example, be acquired by applying a standard format for reporting the methodology, such as the Minimum Information About a Microarray Experiment (MIAME) guidelines [109] or the Minimal Information About T cell Assays (MIATA) standard [110]. In addition, since in vitro stimulations are applied outside the body, those challenges may comprise a less biologically relevant valid representation of real-life immune threats as compared to in vivo challenges, although in vitro immune-related stimulations are easier to implement into the study design.

When focusing on in vivo immune-related challenges, studies on skin tests and wound healing found largest effect sizes and were mostly based on evaluating wound size alteration instead of quantitative immune outcome measures. These outcome parameters contain a rather unidirectional and straightforward representation of immune function (i.e., faster wound healing represents a more optimal immune response). Thus, of all of the immune-related challenges examined, the most convincing evidence was found for stress-reducing psychological interventions optimizing the immune performance in cases of wound healing (medium effect size) and skin-based tests (high effect size). Even though these immune-related challenges probably represent a general stimulation of the immune performance, this could imply that stress-reducing interventions could be particularly clinically relevant for patients with immune-related skin conditions, such as patients recovering from inflammation-sensitive surgical wounds. Contrary to these findings, only a small effect size was found for vaccines. Due to the small number of studies that incorporated a vaccine (5 studies), and variation in the type of incorporated vaccines and the included time points (influenza vaccines, but also 1 study with a hepatitis B vaccine incorporating various measurement points), the present meta-analysis could not provide a conclusive view on this subcategory of in vivo immune-related challenges. As few studies incorporated a vaccine, future research would be helpful to further elucidate the effects of psychological interventions on in vivo immune-related challenges, particularly in the area of vaccination and related immune outcomes.

For studies incorporating psychophysiological challenges, small effect sizes on immune measures were found when incorporating acute challenges (e.g., exam stress), and small effect sizes were found when incorporating chronic stressors (e.g., academic stress). Although the data did not seem to display a high statistical heterogeneity, the incorporated challenges and immune outcome parameters were highly diverse across studies. More specifically, studies included acute challenges such as exams, speech tasks (some accompanied with or without a mental arithmetic task), a treadmill exercise test, and a cold pressor task, as well as more protracted stress challenges such as serostatus notification for individuals undergoing HIV testing and academic stress experienced by students during an examination period. Since the findings of the present study were based on a small number of studies with mostly limited ecological validity of the stressors, i.e., only some included challenges represented chronic stress as experienced by people in daily life, future work should focus on incorporating stressors with a high external validity (e.g., social-evaluative stressors for socially anxious subjects or more daily-life chronic stress such as rumination) in order to evaluate the effects of psychological interventions on immune function [5].

Most the studies that incorporated psychophysiological challenges involved healthy participants (14 out of 17 studies). As healthy participants are supposed to have a well-functioning immune system, they are expected to show responses within the normal range to standard immune system challenges also in absence of a stress-reducing psychological intervention [5]. The challenging situation to which these healthy participants are exposed, therefore, must be powerful enough to detect any relevant alterations in immune function in response to a psychological intervention. It is possible that combination of a psychophysiological challenge with an in vivo immune-related challenge can boost the effects of the separate challenges and possibly provide healthy participants with a more robust immune system challenge. Only 1 study in the present systematic review and meta-analysis combined an in vivo immune-related challenge, i.e., suc-

tion blisters on the volar forearm, with a psychophysiological challenge, i.e., a Trier social stress test, to evaluate the effects of a stress-reducing psychological intervention [55]. In that study, participants who received a stress-reducing mindfulness intervention showed a lower post-stress (i.e., after the Trier social stress test) inflammatory response to the in vivo immune-related and psychophysiological challenges compared to a control group that received a control health enhancement program. The incorporation of both an in vivo immune-related challenge and a psychophysiological challenge provides a more elaborate view of the underlying processes of immune function after a psychological intervention, i.e., evaluating immune function after activation of the immune system through different challenges that can boost each other's effectiveness. Future studies may consider incorporating multiple challenges into their design when examining immune function in healthy participants in order to hypothetically provide them with a rather robust challenge [111].

Regarding the effective components of stress-reducing psychological interventions, no strong conclusions can be drawn at this point due to the substantial heterogeneity in the incorporated intervention elements across studies, including the duration and number of sessions, the intervention target, and ways of guidance (e.g., self-practice, structured guided sessions, etc.). An exploratory evaluation of the data, however, showed that multiple studies explored the role of self-practice during the intervention (e.g., completing homework assignments) for immune outcomes [36, 38, 41, 46, 47, 52, 55, 59, 68, 75, 78, 106]. Most of those studies found a positive association between the frequency of self-practice and optimized immune outcomes [36, 46, 47, 52, 55, 68, 78]. Although we could not formally test this observation in our meta-analysis due to substantial heterogeneity in study designs (e.g., selection of immune outcomes and differences in level of details concerning the specification of self-practice frequency), these findings possibly point to the importance of engaging participants with components of the psychological intervention. However, it is important to note that the studies included in the present systematic review and meta-analysis varied widely in the way in which engagement and the actual effectiveness of the stress-reducing psychological intervention was evaluated.

The clinical relevance of the present findings is that we demonstrated that changes in immune parameters are found following the incorporation of a challenge into the design of the psychological intervention. Therefore, psychological interventions have the potential to alter the immune function which can be relevant to different disorders where immune function is affected. The current findings are in line with previous findings regarding the clinical relevance of altered immune function findings after psychological interventions. More specifically, a study of Antoni et al. [66] in women with breast cancer showed altered cytokine responses after a psychological intervention in response to an in vitro immune-related challenge, suggesting that psychological interventions could optimize the host resistance to cancer. In another study of Antoni et al. [36], they found that a psychological intervention could buffer stress responses after a psychophysiological challenge (i.e., serostatus notification) in patients with HIV. Although the effect sizes in the context of in vitro immune-related challenges were small in the present meta-analysis and no significant effects were found for psychophysiological challenges, in vivo immune-related outcomes showed medium effect sizes. Therefore, the effects of psychological interventions might be less prominent at a cellular level, but it seems to be mainly expressed in response to chemical challenges. Particularly for the in vivo challenges, we found exploratory that the effectiveness of a psychological intervention in allergic participants by exposing them to skin tests yielded highest effect sizes [91–93]. These findings are presumably due to the fact that skin tests provide a rather sensitive immune function parameter in allergic patients. As the results of these studies provide insights not only in that a psychological intervention can alter immune function but also specifically in how a psychological intervention can result in less symptoms for an allergic condition, they aid in the understanding of the extent to which a psychological intervention can possibly support regular treatments for a specific condition, in this case allergic reactions. For this reason, it would be interesting to consider psychological interventions as add-on treatments to conventional medicine in allergic patients to buffer antiallergic responses. As this finding was based on exploratory analyses, future studies should investigate this further and preferably focus on incorporating a challenge that adequately matches the incorporated study sample. We also found a medium effect size for the effectiveness of psychological interventions in wound healing studies. Therefore, psychological interventions may be an effective add-on to conventional medicine, for example for surgery patients to facilitate recovery after a surgical intervention. To reduce the side effects of conventional medicine, it would also be interesting to investigate whether those interventions can at least partially replace

regularly used treatments in, for example, patients with chronic ulcers.

The present meta-analytic review provides a rather comprehensive view on the effectiveness of psychological interventions on optimization of immune function by only incorporating studies that included a challenge into the study design, as more insights are gathered in the actual responsiveness of the immune system in response to a challenge. This not only contributes to the scientific literature but is also interesting for clinical practice. Furthermore, the present meta-analytic review extends the existing knowledge on the effectiveness of mind-body therapies in optimization of immune outcomes. More specifically, a descriptive review on the effectiveness of mind-body therapies in optimization of inflammatory markers already showed promising results [109]. However, mind-body therapies are based on multiple physical and psychological components. By including stress-reducing psychological interventions with cognitive behavior change techniques as the main component in the present meta-analytic review, more insights are gathered in the potential effectiveness of psychological intervention components in optimization of immune function. As the present meta-analytic review overall found a small positive effect of psychological interventions in optimization of immune function, with the highest effect sizes for studies incorporating in vivo immune-related challenges, future research should investigate whether psychological interventions can supplement, or possibly partially replace, current drug treatments in various somatic conditions to reduce side effects.

Besides the above-mentioned strengths, there are a couple of limitations that should be mentioned. First of all, due to the heterogeneity of the incorporated patient samples, psychological interventions, immune outcome parameters, and challenges of the included studies the present meta-analytic review could not provide a conclusive view on the effectiveness of psychological interventions on optimizing immune function. Future studies should systematically incorporate challenges to evaluate the effectiveness of a psychological intervention on immune function and adequately match the incorporated challenge(s) and psychological intervention with the included study population in order to gather a more homogeneous view on this topic. Second, we found additional studies based on screening of the reference lists of the included studies that were not identified in the primary search. Most of these studies did not specify immune outcome measures in the title and/or abstract. We cannot rule out that more studies were omitted in the present meta-analytic review due to a lack of sufficient specificity on the incorporation of immune outcome parameters in the title and/or abstract. It is important for future studies to specify immune outcome measures specifically in the title and/or abstract to ensure that they can be detected in searches. In addition, future systematic reviews and meta-analysis should be aware that some studies can be overlooked (i.e., in the case of studies that assess immune function without immune outcome parameters, as can be the case in wound healing studies) when including the immune outcome parameters as a category in their search. Therefore, a more general search term may be preferable when providing a systematic search on this topic. Third, a substantial number of studies did not report on whether the intervention was actually effective in reducing stress, making it hard to take this factor into account in our analyses. For the same reason, it was not possible to control for confounding factors, including BMI, recent illness, female menstruation cycle, and so on. As failures to improve immunity can be due to the fact that the stress-reducing psychological interventions were actually not effective in reducing stress, future studies should also carefully evaluate to what extent participants were engaged with the stress-reducing psychological intervention and whether these interventions were effective in reducing stress. To optimize the methodological aspects of the study design, future studies should take into account the recommendations of a recent review [112]. Finally, the present findings were based on the assumption that higher levels of immune activation were associated with a more optimized immune response. However, enhanced immune responses are not necessarily beneficial, e.g., in the case of inflammatory and autoimmune disorders, making it important to take the type of immune response into account [113]. In certain cases, optimization is not based on larger immune responses but rather on normalization of immune outcomes, making it hard to assess optimized immune function as a linear function and to compare various types of immune outcome parameters. Future studies should therefore take the incorporated immune parameters and the type of response, as well as the studied population, into account when evaluating the effectiveness of a psychological intervention on immune function. Note that, as the aim of a stress-reducing psychological intervention is to optimize health outcomes by stress reduction, it would be relevant to recruit individuals who experience chronic stress with a substantial impact on immune function to evaluate the effectiveness of stress-reducing psychological interventions [22]. In addition, future studies should focus on unraveling the effec-

tive intervention components in optimization of immune responses by evaluating the effectiveness of intervention components separately but also in combination with each other.

In conclusion, the present systematic review and meta-analysis provided evidence for the effects of stress-reducing interventions in optimization of immune function when immune outcomes were evaluated using tests that apply challenges to the immune system. While consistent evidence came from studies that evaluated immune function through an in vivo immune-related challenge, specifically studies incorporating skin tests and studies on wound healing, similar but smaller effect sizes were found for in vitro immune-related stimulations and immune responses to psychophysiological challenges. Due to the large heterogeneity in study designs, there is a need for future research that incorporates immune- and psychophysiological challenges, as these have a high external validity and are suitable for possible clinical applications in immune-related diseases. Studies in healthy participants have to make sure that the immune challenge is robust enough, e.g., by combining separate challenges. Finally, future studies should carefully report on the methodological details according to standardized guidelines, including the actual stress-reducing effectiveness of the psychological interventions, and appropriate interpretation of the immune outcomes. This can result in further insights into the immune outcomes that are responsive to change as well as a thorough view on the effective intervention components to optimize immune responses in the short and longer term.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interests to declare.

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Author Contributions

Study conception and design: L.S., D.S.V., H.v.M., and A.W.M.E. Acquisition of data: L.S., D.S.V., P.I.C., and J.A.B. Analysis and interpretation of the data and writing of this paper: L.S., D.S.V., P.I.C., J.A.B., S.C., S.A.J., L.G.V, T.H.M.O., and A.W.M.E. All of the authors approved the submission of the final version of this paper.

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